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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/676,834	09/29/2000	Michael Z. Gilman	APBI-P04-340	4232

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EXAMINER	
KAUSHAL, SUMESH	
ART UNIT	**PAPER NUMBER**
1636	

DATE MAILED: 10/18/2004

Please find below and/or attached an Office communication concerning this application or proceeding.

Advisory Action	Application No.	Applicant(s)	
	09/676,834	GILMAN, MICHAEL Z.	
	Examiner	Art Unit	
	Sumesh Kaushal Ph.D.	1636	

--The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

THE REPLY FILED 19 July 2004 FAILS TO PLACE THIS APPLICATION IN CONDITION FOR ALLOWANCE. Therefore, further action by the applicant is required to avoid abandonment of this application. A proper reply to a final rejection under 37 CFR 1.113 may only be either: (1) a timely filed amendment which places the application in condition for allowance; (2) a timely filed Notice of Appeal (with appeal fee); or (3) a timely filed Request for Continued Examination (RCE) in compliance with 37 CFR 1.114.

PERIOD FOR REPLY [check either a) or b)]

a) ☐ The period for reply expires _____months from the mailing date of the final rejection.

b) ☐ The period for reply expires on: (1) the mailing date of this Advisory Action, or (2) the date set forth in the final rejection, whichever is later. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the mailing date of the final rejection. ONLY CHECK THIS BOX WHEN THE FIRST REPLY WAS FILED WITHIN TWO MONTHS OF THE FINAL REJECTION. See MPEP 706.07(f).

Extensions of time may be obtained under 37 CFR 1.136(a). The date on which the petition under 37 CFR 1.136(a) and the appropriate extension fee have been filed is the date for purposes of determining the period of extension and the corresponding amount of the fee. The appropriate extension fee under 37 CFR 1.17(a) is calculated from: (1) the expiration date of the shortened statutory period for reply originally set in the final Office action; or (2) as set forth in (b) above, if checked. Any reply received by the Office later than three months after the mailing date of the final rejection, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

1.☒ A Notice of Appeal was filed on *19 July 2004*. Appellant's Brief must be filed within the period set forth in 37 CFR 1.192(a), or any extension thereof (37 CFR 1.191(d)), to avoid dismissal of the appeal.

2.☐ The proposed amendment(s) will not be entered because:

(a) ☐ they raise new issues that would require further consideration and/or search (see NOTE below);

(b) ☐ they raise the issue of new matter (see Note below);

(c) ☐ they are not deemed to place the application in better form for appeal by materially reducing or simplifying the issues for appeal; and/or

(d) ☐ they present additional claims without canceling a corresponding number of finally rejected claims.

NOTE: _____.

3.☐ Applicant's reply has overcome the following rejection(s): _____.

4.☐ Newly proposed or amended claim(s) _____ would be allowable if submitted in a separate, timely filed amendment canceling the non-allowable claim(s).

5.☒ The a)☐ affidavit, b)☐ exhibit, or c)☒ request for reconsideration has been considered but does NOT place the application in condition for allowance because: *See Continuation Sheet*.

6.☐ The affidavit or exhibit will NOT be considered because it is not directed SOLELY to issues which were newly raised by the Examiner in the final rejection.

7.☒ For purposes of Appeal, the proposed amendment(s) a)☐ will not be entered or b)☒ will be entered and an explanation of how the new or amended claims would be rejected is provided below or appended.

The status of the claim(s) is (or will be) as follows:

Claim(s) allowed: _____.

Claim(s) objected to: _____.

Claim(s) rejected: *1-3,5-14 and 16-38*.

Claim(s) withdrawn from consideration: *6-13,16 and 21-23*.

8.☐ The drawing correction filed on _____ is a)☐ approved or b)☐ disapproved by the Examiner.

9.☐ Note the attached Information Disclosure Statement(s)(PTO-1449) Paper No(s). _____.

10.☐ Other: _____

JEFFREY FREDMAN
PRIMARY EXAMINER

Continuation of 5. does NOT place the application in condition for allowance because:

Claims 1, 3, 5, 14, 17, 18, 20 and 24-38 stand rejected under 35 U.S.C. 103(a) as being unpatentable over US 5,654,168 (Bujard et al., of record) in view of US 5,639,725 (O'Reilly et al) for the same reasons of record as set forth in the office action mailed on 01/16/04.

Bujard et al. teaches an inducible regulatory system for control of transcription comprising (see especially the summary, columns 9-15, 18, 19, 27 and 29) a genetic construct encoding a chimeric protein, which is useful for the regulation of transcription of a target gene, and a construct encoding the target gene. The chimeric protein consists of a ligand binding domain and a heterologous domain, which binds to the transactivation domain of a target gene. The chimeric protein is expressed in a cell. The chimeric protein binds to a ligand (antibiotic). Upon ligand binding to the chimeric protein, the chimeric protein binds to a transactivating region on a target gene thereby regulating the expression of the target gene, which may be an anti-angiogenesis factor (see col. 29, lines 26-55). The regulation may be performed in a host organism, which may be a human (see col. 27, lines 28-46). The genetic construct and the target gene may be introduced into the cell by a viral vector (see cols. 1 1-12 and col. 14, line 61-col. 15, line 17). Numerous cell types are described (see col. 13, lines 53-64). Selectable markers may be used (see col. 14, lines 29-53). Claimed Kd values and molecular size is taught (see col. 26, bottom). The ligand-binding domain is contained in a 207 amino acid protein (see column 6, line l6-column 9, line 26). The regulation of the transcription of the target gene is controlled by the presence or absence of the antibiotic ligand, thereby inducibly regulating the transcription of the desired target (anti-angiogenesis) gene. Bujard et al. does not teach that the anti-angiogenesis factor (col. 29, lines 26-55) is the angiostatin gene.

O'Reilly et al. teach the angiostatin protein at the abstract and throughout the specification, which is an anti-angiogenesis factor useful for instance in inhibiting angiogenesis in tumor growth. O'Reilly teaches at the summary and columns 6-10, the transcription and expression of an angiostatin gene in vitro and in vivo. O'Reilly teaches at column 9, the desirable and useful expression of the angiostatin gene in an appropriate vector for inhibition of undesired and uncontrolled angiogenesis, such as occurs in cancer and tumors. O'Reilly et al. teach at columns 3 and 4 that tumor growth is dependent upon angiogenesis, and that angiogenesis is essential and desirable for wound healing, and for fetal and embrmnal development for example. It is therefore desirable to inhibit angiogenesis in a specific and controlled manner. Angiostatin is taught to be useful for inhibition of angiogenesis with minimal side effects (see column 5).

It would have been obvious to one of ordinary skill in the art at the time the instant invention was made to inducibly control the expression of angiostatin by modifying the target gene encoding an anti-angiogenesis factor taught by Bujard et al. by using the gene encoding angiostatin (an anti-angiogenesis factor) of O'Reilly et al for the expected benefit of expressing the angiostatin gene in a controlled manner to specifically inhibit unwanted angiogenesis, especially angiogenesis related to tumor growth, with minimal side effects. Further, a person of ordinary skill in the art would have had a reasonable expectation of success in the producing the instant claimed invention given the teachings of Bujard and O'Reilly who demonstrate the expression of an anti-angiogenesis factor in cells in-vitro and in-vivo.

Response to arguments

Applicants reiterate the arguments of record regarding this ground of rejection, and contend that the cited references fail to satisfy the criteria necessary for rendering the claimed invention obvious. However, applicant's arguments are found NOT fully persuasive since instant claims stand rejected for the same reasons of record as set forth in the office action mailed on 01/16/04 and as repeated below.

The applicant fails to consider the combined teaching of the reference cited herein in entirety. The combination and modification of the teachings of the prior art clearly suggested the claimed invention. The arguments taken as a whole rely heavily on the deficiencies of each reference taken alone. One cannot show non-obviousness by attacking references individually where the rejections are based on combinations of references. *In re Keller*, 642 F.2d 413, 208 USPQ 871 (CCPA 1981); *In re Merck & Co., inc.*, 800 F.2d 1091, 231 USPQ 375 (Fed. Cir. 1986). In instant case the combined teaching of clearly teaches all the components of invention as claimed. Bujard teaches an inducible regulatory system which

is useful for the regulation of transcription of a target gene. Even though Bujard does not specifically teaches angiostatin, the cited art clearly suggest that the gene of particular interest to be expressed in cells of a subject for the treatment of a genetic or acquired disease include anti-angiogenesis factors (see col.29 lines 25-37). Furthermore, O'Reilly specifically teaches that angiostatin is an anti-angiogenesis factor, which is useful for the inhibition of angiogenesis in tumors. Therefore considering the combined teaching in the cited prior art of record, it would have been obvious to substitute the gene of interest in the inducible regulatory system as taught by Bujard with an angiostatin gene in view of O'Reilly. One would have a reasonable expectation of success, since substitution of gene of interest in an expression vector has been routine in the art at the time of filing. Thus the invention as claimed is obvious in view of prior art of record.

Claims 1-3, 5, 14, 17-20 and 24-38 stand rejected under 35 U.S.C. 103(a) as being unpatentable over Bujard et al and O'Reilly et al as applied to claims 1, 3, 5, 14, 17, 18, 20 and 24-38 above, and further in view of WO 94/18317 (Crabtree et al, ref. of record), for the same reasons of record as set forth in the office action mailed on 01/16/04.

Bujard and O'Reilly teach the invention as described above. However Bujard and O'Reilly do not teach that the transcription of the angiostatin gene may be responsive to dimerization of the chimeric protein in the presence of the ligand, nor that the LBD may be an immunophilin ligand binding domain, a cyclophilin ligand binding domain or a steroid receptor binding domain.

Crabtree et al. teach (see especially pages 6-7) the equivalence of an antibiotic binding domain, a cyclophilin ligand binding domain or a steroid binding domain to practice a method of the invention. Crabtree et al. teach a method of regulating expression of a target gene by exposing a cell to a ligand. The cell is transfected with a genetic construct encoding a chimeric protein comprising a ligand binding domain and a second domain, and which is also transfected with a target gene that is transcriptionally responsive to the chimeric protein when the chimeric protéin is bound to a ligand. The ligand binds to ligand binding domains in chimeric proteins expressed from the genetic constructs. While the ligand is bound to the ligand binding domains of the chimeric proteins, the ligand-chimeric protein complex binds to a transactivating region operatively linked to the target gene. The binding of the ligand-chimeric proteins complex to the transactivating region of the target gene regulates the expression of the target gene, both in vitro and in vivo. The ligand-bound chimeric proteins may dimerize or multimerize to effect the regulation of the target gene. Crabtree et al. teach at pages 12-16, that there are multiple types of expression regulation chimeric proteins available to one of ordinary skill in the art, and that each type of expression regulating chimeric protein may operate in a dimerized or multimerized manner. Each type of chimeric regulating protein may be bound by a unique ligand. Each ligand/chimeric protein combination may be used to regulate a desired target gene in a specific cell or cellular compartment. Dimerization or multimerization also results in higher binding affinity of the chimeric protein for its responsive sequence in the target gene (see page 30, lines 15-33).

It would have been obvious to one of ordinary skill in the art, at the time the instant invention was made, to modify the ligand-binding of the chimeric protein, which induces expression of the desired anti-angiogenesis factor as taught by Bujard with the ligand binding which induces dimerizing and multimerizing of the chimeric protein, where the dimerized or multimerized chimeric protein induces expression of the desired gene as taught by Crabtree for the expected benefit of expressing the angiostatin gene to inhibit angiogenesis using different ligands to bind chimeric regulating proteins, in different cell types or cellular compmments with higher affinity for the responsive sequence in the desired target gene as taught by Crabtree. Further, a person of ordinary skill in the art would have had a reasonable expectation of success in the producing the instant claimed invention given the teachings of Bujard, O'Reilly. and Crabtree who demonstrate the regulation of expression of a target gene in cells in vitro and in vivo.

Response to arguments

Applicants reiterate the arguments of record regarding this ground of rejection, and contend that the cited references fail to satisfy the criteria necessary for rendering the claimed invention obvious.

However, applicant's arguments are found NOT fully persuasive since instant claims stand rejected for the same reasons of record as set forth in the office action mailed on 01/16/04 and as repeated below.

However, this is found NOT persuasive because the applicant fails to consider the combined teaching of the reference cited herein in entirety. The combination and modification of the teachings of the prior art clearly suggested the claimed invention. The arguments taken as a whole rely heavily on the deficiencies of each reference taken alone. One cannot show non-obviousness by attacking references individually where the rejections are based on combinations of references. *In re Keller*, 642 F.2d 413, 208 USPQ 871 (CCPA 1981); *In re Merck & Co., Inc.*, 800 F.2d 1091, 231 USPQ 375 (Fed. Cir. 1986). The obviousness can only be established by combining or modifying the teachings of the prior art to produce the claimed invention where there is some teaching, suggestion, or motivation to do so found either in the references themselves or in the knowledge generally available to one of ordinary skill in the art. See *In re Fine*, 837 F.2d 1071, 5 USPQ2d 1596 (Fed. Cir. 1988) and *In re Jones*, 958 F.2d 347, 21 USPQ2d 1941 (Fed. Cir. 1992).

In instant case the combined teaching of clearly teaches all the components of invention as claimed. Bujard teaches an inducible regulatory system which is useful for the regulation of transcription of a target gene. Even though Bujard does not specifically teaches angiostatin, the cited art clearly suggest that a gene of particular interest to be expressed in cells of a subject for the treatment of a genetic or acquired disease include anti-angiogenesis factors (see col.29 lines 25-37). Furthermore, O'Reilly specifically teaches that angiostatin is an anti-angiogenesis factor, which is useful for the inhibition of angiogenesis in tumors. Therefore considering the combined teaching in the prior art of record, it would have been obvious to substitute the gene of interest in the inducible regulatory system as taught by Bujard with the angiostatin gene in view of O'Reilly. It would have been further obvious to one ordinary skill in the art to modify the ligand-binding of the chimeric protein, which induces expression of the desired anti-angiogenesis factor as taught by Bujard with the ligand binding which induces dimerizing and multimerizing of the chimeric protein, where the dimerized or multimerized chimeric protein induces expression of the desired gene in view of Crabtree. Thus the invention as claimed is prima facie obvious in view of cited prior art.